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(54) Title: ANTHELMINTIC COMPOSITION

(57) Abstract: The invention relates to the treatment of anthelmintic infections in animals, and more particularly to compositions that are effective against parasites that are resistant to a wide variety of drug treatments. In a first aspect, the invention provides a synergistic anthelmintically effective composition consisting of at least one compound selected from each of the following groups: macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles and a therapeutically acceptable carrier. In a second aspect, the invention provides a method for treating parasitic infections in an animal, comprising administering to the animal, a synergistic anthelmintically effective amount of a composition which consists of at least one compound selected from each of the following groups: macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles and a therapeutically acceptable carrier. In a third aspect, the invention provides the use of a synergistic anthelmintically effective amount of a composition which consists of at least one compound selected from each of the following groups: macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles and a therapeutically acceptable carrier in the treatment of a parasitic infection in an animal.

ANTHELMINTIC COMPOSITION

Field of the Invention

This invention relates to the treatment of anthelmintic infections in animals, and more particularly to compositions that are effective against parasites that are resistant to a wide variety of drug treatments, particularly in non-human animals..

Background to the Invention

Farm animals such as lambs, weaners and sheep may typically be infected by a wide variety of parasites. Such parasites include *Haemonconchus spp., Ostertagia spp., Trichostrongylus spp., Cooperia spp., Nematodirus spp., Chabertia spp., Oesophagostomum spp., Trichuris spp., Strongyloides spp., Bunostomum spp., Oestrus spp., Dictyocaulus spp., Fasciola spp. and Monezia spp.* Specific examples of these parasites are set out in Table 1.

For a variety of reasons, there is an increasing number of such parasites that have developed resistance to available drug treatments. Moreover, because of the infective nature and ready transmission from animal to animal, the presence of resistant parasites will rapidly spread to infect a substantial number, if not all, of the animals in a flock or herd. One means by which such infection will rapidly spread is where new animals in which the presence of drug resistance is known or suspected are to be introduced onto a property.

There are a variety of drug substances that are used to treat parasitic infections. Amongst these broad groups of substances are macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles. Unfortunately, many of the parasites mentioned in Table 1 have developed resistance to these substances.

Although the problem of resistance has been tackled through the development of new substances, the time to develop, evaluate and demonstrate efficacy of such substances is substantial and expensive. Moreover for the reasons that resistance has developed against existing substances it is very likely that resistance will occur in relation to these new substances.

Summary of the Invention

Rather then tackling the problem of resistance through the development of new substances, the present inventors have found that it is possible to circumvent resistance by combining specific classes of anthelmintics. The efficacy of this combination arises out of the finding that the combination is synergistic.

Accordingly, the present invention provides in a first aspect, a synergistic anthelmintically effective composition consisting of at least one compound selected from each of the following groups: macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles and a therapeutically acceptable carrier.

Table 1 Parasite Species

Species	Common Name	Comments
Haemonchus contortus	Barber's pole worm	includes inhibited L4 stage
Haemonchus placei	Large stomach worm	
Ostertagia circumcincta	Small brown stomach worm	includes inhibited L4 stage
Trichostrongylus axei	Stomach hair worm	
Trichostrongylus colubriformis		
Trichostrongylus vitrinus	Black scour worm	
Cooperia curticel		
Cooperia oncophera	Small intestinal worm	
Nematodirus spathiger		
Nematodirus filicollis	Thin-necked intestinal worm	
Chabertia ovina	Large mouthed bowel worm	
Oesophagostomum columbianum	Nodule worm	

Oesophagostomum venulosum	Large bowel worm	
Trichuris ovis	Whip worm	
Strongyloides papillosus	Intestinal threadworm	
Bunostomum spp	Hookworm	
Oestrus ovis		
Dictyocaulus viviparus	Large lungworm	
Fasciola hepatica		
Monezia		Includes head and segments

In a second aspect, the present invention provides a method for treating parasitic infections in an animal, comprising administering to the animal, a synergistic anthelmintically effective amount of a composition which consists of at least one compound selected from each of the following groups: macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles and a therapeutically acceptable carrier.

In a third aspect, the present invention further provides the use of a synergistic anthelmintically effective amount of a composition which consists of at least one compound selected from each of the following groups: macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles and a therapeutically acceptable carrier in the treatment of a parasitic infection in an animal.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

The aforementioned treatments may be desirably administered to animals prior to introduction to a land area so as to prevent the land area from becoming infested with parasites which may or may not be resistant to one or more compounds selected from the groups consisting of macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles. Typically, animals such as sheep, will be isolated for at least 2 days after treatment before being placed on pasture.

Alternatively, animals may be treated at any time, as appropriate, particularly when it is suspected that the animal may be carrying at least one parasite which is resistant to at least one of the groups macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles.

The compositions of this invention have application where the parasites are resistant to known drug treatments. In particular, the compositions are effective in situations where parasites are resistant to at least one of each of the groups macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles. Preferably, the compositions are effective in situations where parasites are resistant to at least two of each of the groups macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles. More preferably, the compositions are effective in situations where parasites are resistant to at least three of each of the groups macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles. Most preferably, the compositions are effective in situations where parasites are resistant to all of the groups macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles.

In use, a preferred indication is the treatment of stock to eliminate adult gastro-intestinal worms and liver fluke. Typically, treatment results in the clearance of >95% of total worm count including worms resistant to at least one of each of the groups macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles.

Compositions of this invention include at least one compound selected from each of the groups: macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles.

Representative examples of compounds from each of these group are set out in Table 2.

Table 2 Compounds

Macrocyclic lactone	Benzimidazole	Salicylanilide	Imidazothiazole
abamectin	albendazole	closantel	levamisole
ivermectin	fenbendazole	niclosamide	pyrantel pamoate
doramectin	thiabendazole		butamisole
moxidectin	oxfenbendazole		
cydectin	fenbantel		
milbenycin	mebendazole		
	parbendazole		
	flubendazole		
	oxibendazole		
	carbendazole		

Of these combinations which include at least abamectin from the macrocylic lactone group together with one compound from each of the other three groups; at least albendazole from the benzimidazole group together with one compound from each of the other three groups; closantel together with one compound from each of the other three groups and levamisole together with one compound from each of the other three groups are each preferred. Particularly preferred is the specific combination of abamectin, albendazole, closantel and levamisole. Most preferably, the levamisole is used in the form of a water soluble salt such as the hydrochloride.

The therapeutically active compounds used in the invention are preferably incorporated into formulations in the range of concentrations as follows (g/L)

macrocylic lactones: 0.1-20.0 g/L, preferably 0.5-1.5 g/L
benzimidazoles: 1-100 g/L, preferably 18-30 g/L
salicylanilides: 1-100 g/L, preferably 30-50 g/L
imidazothiazoles: 1-100 g/L, preferably 30-50 g/L

Although drenches are preferred dosage forms for the compositions of this invention, a number of alternative compositions may be used. These pour-on transdermals, slow release boluses for rumenal deposition and injectable formulations.

Each dosage form requires a therapeutically effective carrier. In the case of drenches, typically a formulation will include a solvent system for the macrocylic lactones, one or more dispersing and suspending agents for the benzimidazoles and salicylanilides , one or more surfactants, one or more preservatives, a buffering system and water as a carrier.

The solvent system for the macrocyclic lactones includes at least one solvent selected from the group consisting of: polyethylene glycol, tetraglycol, ethanol, benzyl alcohol and propylene glycol.

The dispersing and suspending agents for the benzimidazoles and salicylanilides include at least one selected from the group consissting of: glyceryl palmitostearate, bentonite, colloidal silica, xanthan gum and polymeric pyrrolidones.

Surfactants that may be used include polysorbate 80 and ethoxylated castor oil.

A variety of buffer systems may be used, particularly phosphate buffers based on combinations of varying amounts of monobasic and dibasic sodium phosphate to achieve the desired pH.

The compositions of the invention are effective when used in a variety of animals. For example, sheep, goats, ruminants (including cattle) and camelids.

Modes for Carrying Out the Invention

In order to better understand the nature of the invention, a number of examples will now be described as follows:

Example 1

Material	Supplier	Grade	Amount (g)
Avermectin	Haiman	Technical 94%	1.0
Albendazole	Pacific Resource	USP24	25.0
Closantel	Pacific Resource	Technical 98%	37.5
Levamisole Hydrochloride	Pacific Resource	BP 1998	40.0
Tetraglycol	AGRAR	Food Grade	400.0
Benzyl alcohol	APS	BP1998	80.0
Keltrol F	(Xanthan Gum) Rhone-Poulenc	USP24	10.0
Phenonip	(Phenoxyethanol) Bronson& Jacobs	Food	10.0
Glyceryl Palmitostearate	(Precirol ATO 5) Bronson & Jacobs	USP24	5.0
Veegum Regular	(Magnesium Aluminium Silicate) RT Vanderbilt Co.	USP24	-
PVP29/30	(Ethenyl-2-pyrrolidinone homopolymer) ISP	USP24	-
PVP C15	ISP	USP24	-
Polyethylene glycol	(PEG 2000) BASF	USP24	-
Cremophor	(ethoxylated Castor Oil) BASF	USP24	-
Propylene Glycol		USP24	-
Sodium phosphate monobasic	Bronson & Jacobs	Technical	-
Sodium phosphate dibasic	Bronson & Jacobs	Technical	-
Polysorbate 80	Bronson & Jacobs	USP24	-
Cab-O-Sil M5	(Colloidal Silicon Dioxide) Cabot Corp	USP24	-
Water			qs 1litre

Example 2

Material	Supplier	Grade	Amount (g)
Avermectin	Haiman	Technical 94%	0.8
Albendazole	Pacific Resource	USP24	19.0
Closantel	Pacific Resource	Technical 98%	30.0
Levamisole Hydrochloride	Pacific Resource	BP 1998	35.5
Glycerol formal			30.0
Tetraglycol	AGRAR	Food Grade	-
Ethanol			20.0
Benzyl alcohol	APS	BP1998	80.0
Keltrol F	(Xanthan Gum) Rhons-Poulenc	USP24	10.0
Phenonip	(Phenoxyethanol) Bronson& Jacobs	Food	-
Potassium sorbate			10.0
Glyceryl Palmitostearate	(Precirol ATO 5) Bronson & Jacobls	USP24	-
Veegum Regular	(Magnesium Aluminium Silicate) RT Vanderbilt Co	USP24	50.0
PVP29/30	(Ethenyl-2-pyrrolidinone homopolymer) ISP	USP24	50.0
PVP C15	ISP	USP24	-
Polyethylene glycol	(PEG 2000) BASF	USP24	-
Cremophor	(ethoxylated Castor Oil) BASF	USP24	-
Propylene Glycol		USP24	-
Sodium phosphate monobasic	Bronson & Jacobs	Technical	-
Sodium phosphate dibasic	Bronson & Jacobs	Technical	-
Polysorbate 80	Bronson & Jacobs	USP24	-
Cab-O-Sil M5	(Colloidal Silicon Dioxide) Cabot Corp	USP24	-
Water			qs 1litre

Example 3

Material	Supplier	Grade	Amount (g)
Avermectin	Haiman	Technical 94%	1.0
Albendazole	Pacific Resource	USP24	25.0
Closantel	Pacific Resource	Technical 98%	37.5
Levamisole Hydrochloride	Pacific Resource	BP 1998	40.0
Tetraglycol	AGRAR	Food Grade	-
Benzyl alcohol	APS	BP1998	20.0
Keltrol F	(Xanthan Gum) Rhone-Poulenc	USP24	-
Phenonip	(Phenoxyethanol) Bronson& Jacobs	Food	20.0
Glyceryl Palmitostearate	(Precirol ATO 5) Bronson & Jacobs	USP24	-
Bentonite			20.0
Veegum Regular	(Magnesium Aluminium Silicate) RT Vanderbilt Co.	USP24	-
PVP29/30	(Ethenyl-2-pyrrolidinone homopolymer) ISP	USP24	-
PVP C15	ISP	USP24	100.0
Polyethylene glycol	(PEG 2000) BASF	USP24	-
Cremophor	(ethoxylated Castor Oil) BASF	USP24	80.0
Propylene Glycol		USP24	-
Sodium phosphate monobasic	Bronson & Jacobs	Technical	-
Sodium phosphate dibasic	Bronson & Jacobs	Technical	-
Polysorbate 80	Bronson & Jacobs	USP24	-
Cab-O-Sil M5	(Colloidal Silicon Dioxide) Cabot Corp	USP24	-
Water			qs 1litre

Example 4

Material	Supplier	Grade	Amount (g)
Avermectin	Haiman	Technical 94%	1.0
Albendazole	Pacific Resource	USP24	25.0
Closantel	Pacific Resource	Technical 98%	37.5
Levamisole Hydrochloride	Pacific Resource	BP 1998	40.0
Tetraglycol	AGRAR	Food Grade	-
Benzyl alcohol	APS	BP1998	80.0
Keltrol F	(Xanthan Gum) Rhone-Poulenc	USP24	-
Phenonip	(Phenoxyethanol) Bronson& Jacobs	Food	-
Glyceryl Palmitostearate	(Precirol ATO 5) Bronson & Jacobs	USP24	-
Veegum Regular	(Magnesium Aluminium Silicate) RT Vanderbilt Co.	USP24	-
PVP29/30	(Ethenyl-2-pyrrolidinone homopolymer) ISP	USP24	-
PVP C15	ISP	USP24	-
Polyethylene glycol	(PEG 2000) BASF	USP24	-
Cremophor	(ethoxylated Castor Oil) BASF	USP24	-
Propylene Glycol		USP24	300.0
Sodium phosphate monobasic	Bronson & Jacobs	Technical	9.0
Sodium phosphate dibasic	Bronson & Jacobs	Technical	1.0
Polysorbate 80	Bronson & Jacobs	USP24	200.0
Cab-O-Sil M5	(Colloidal Silicon Dioxide) Cabot Corp	USP24	200.0
Water			qs 1litre

Example 4 was prepared as follows:

1. Dissolve avermectin in benzyl alcohol and propylene glycol.
2. Add polysorbate 80 to step 1.
3. Add water to the solution from step 2 and mix until homogeneous.
4. Dissolve sodium phosphate dibasic and sodium phosphate monobasic in the solution from step 3.
5. Add closantel, albendazole and levamisole hydrochloride. Mix until fully dispersed.
6. Add Cab-O-Sil M5 to the suspension and homogenise until the thicken agent fully hydrated.

Based on this disclosure, the person skilled in the art would appreciate the general approach to be taken in preparing the compositions of this invention.

In order evaluate the efficacy of the compositions of the invention, a number of trials were conducted using Example 4 as above.

Trial RD0201-H002: A critical pen sacrifice study evaluating the therapeutic efficacy of a combination abamectin, levamisole hydrochloride, albendazole and closantel anthelmintic formulation against resistant strains of *Haemonchus contortus*, *Trichostrongylus colubriformis* and *Teladorsagia circumcincta* in sheep.

This study was conducted from the 25th of February to the 29th of August, 2002, with the animal phase conducted from the 7th May to the 27th June 2002. Suitable sheep (18) were relocated to the University of New England Animal House Facility on the 7th May 2002 were weighed, identified with individually numbered ear tags and treated with twice the recommended dose rate of Ivomec (Liquid for Sheep, Merial Australia Pty Ltd), to remove any residual worm burden.

On 22nd May 2002 (Day -26) faecal samples were collected from each trial animal to confirm individual zero faecal egg counts. Later that day trial sheep were infected with approximately 5000 *Haemonchus contortus* (macrocyclic lactone and closantel resistant strains), 6000 *Trichostrongylus colubriformis* (levamisole hydrochloride and albendazole resistant strains) and 5000 *Osteratagia circumcincta* (macrocyclic and albendazole resistant strains) infective larvae.

Faecal samples were collected from each sheep on 14th June 2002 (Day -3) and individual faecal egg counts were conducted. Animals were ranked on the basis of decreasing faecal egg counts and blocked into eight blocks each of two animals and randomly allocated to the treatment groups from these blocks. The 16 animals with the highest counts were selected for inclusion in the trial and the two animals with the lowest faecal egg counts were selected as spare animals.

On 17th June 2002 (Day 0) all trial animals were weighed, faecal sampled and animals in Group 2 were treated as follows. Animals were weighed and dosed according to individual live weight as outlined in Table 3.

Table 3: Dosage regime

	Treatment	Dose rate	Active Ingredient
Group 1	Untreated control	-	-
Group 2	Example 4	1 mL/5 kg	37.5 g/L closantel g/L abamectin 40 g/L levamisole hydrochloride 25 g/L albendazole

The 18 trial sheep (including the 2 spare animals) were sacrificed on 27th June 2002 (Day 10) for collection of faecal samples, abomasal and small intestine contents. Individual faecal egg counts, treatment group coprocultures and total worm counts were conducted for calculation of treatment efficacies.

Drenchrites (CSIRO Research - Horizon Technology 1996) was performed between the 10th July and the 23rd August 2002 to clarify that strains of *Trichostrongylus colubriformis* used were resistant to levamisole hydrochloride and albendazole and, *Osteratagia circumcincta* were resistant to albendazole.

Faecal samples were collected according to standard procedures and submitted to the Veterinary Health Research parasitological laboratory. Individual strongyle faecal egg counts and group bulk coproculture for larval differentiation were carried out. Gastrointestinal tracts were recovered according to standard procedures and following gut washing were submitted to the parasitological laboratory. Individual total worm counts were conducted and results are summarised in the accompanying tables, 4-10 and figures 1-4.

Table 4: Group mean strongyle faecal egg counts.

Group	Treatment	Day 0	Day 10
		Arithmetic Means	
1	Control	9320.0[1]	8568.9
2	Example 4	8177.8[1]	22.2
		Geometric Means	
1	Control	6754.5	6754.5[1]
2	Example 4	1.8	1.8[2]

[1] Means with different superscripts within the same column are significantly different at $p<0.05$

Table 5: Percentage reduction of strongyle species (based on group mean strongyle faecal egg count data)

Group	Treatment	Day 10
		Arithmetic Efficacy
2	Example 4	99.7%
		Geometric Efficacy
2	Example 4	>99.9%

Table 6: Group mean abomasal Total Worm Counts

Group	Treatment	Slaughter Day	Number	*Haem*[a] (adults)	*Haem* (imm)[d]	*Oster*[b] (adults)	*Oster* (imm)	*Oster* (L4)[c]
				Arithmetic Means				
1	Control	10	9	3006.7	15.6	1913.3	24.4	33.3
2	Example 4	10	9	0.0	0.0	0.0	0.0	0.0
				Geometric Means				
1	Control	10	9	2683.1^1	2.5^1	1850.6^1	4.7^1	7.7^1
2	Example 4	10	9	0.4^2	0.0^1	0.0^2	0.0^1	0.0^2

Note: Example 4 = abamectin / closantel /albendazole /levamisole hydrochloride

[a] Haemonchus species; [b] Ostertagia species; [d] imm = immature; [c] L4 = fourth larval stage

[1] Means with different superscripts within the same column are significantly different at $p<0.05$

Table 7: Percentage reduction of abomasal worms (based on Total Worm Counts)

Group	Treatment	Slaughter Day	Number	*Haem*[a] (adults)	*Haem* (imm)[d]	*Oster*[b] (adults)	*Oster* (imm)	*Oster* (L4)[c]
				Arithmetic Efficacies				
2	Example 4	10	9	>99.9%	>99.9%	>99.9%	>99.9%	>99.9%
				Geometric Efficacies				
2	Example 4	10	9	>99.9%	>99.9%	>99.9%	>99.9%	>99.9%

[a] Haemonchus species; [b] Ostertagia species; [d] imm = immature; [c] L4 = fourth larval stage

Table 8: Group mean small intestinal Total Worm Counts

Group	Treatment	Slaughter Day	Number	*Trichs*[a] (adults)	*Trichs* (imm)	*Nem* (adults)	*Nem*[c] (imm)[d]	*Coop*[e] (adults)	*Coop*[e] (imm)[d]
				Arithmetic means					
1	Control	10	9	2791.1	6.7	0.0	0.0	0.0	0.0
2	Example 4	10	9	0.0	0.0	0.0	0.0	0.0	0.0
				Geometric means					
1	Control	10	9	2018.9[1]	1.1[1]	0.0	0.0	0.0	0.0
2	Example 4	10	9	0.0[2]	0.0[1]	0.0	0.0	0.0	0.0

[a] Trichostrongyle species; [c] Nematodirus species; [d] imm = immature; [e] Cooperia species

[1] Means with different superscripts within the same column are significantly different at $p<0.05$

Table 9: Percentage reduction of small intestinal worms (based on Total Worm Counts)

Group	Treatment	Slaughter Day	Number	*Trichs*[a] (adults)	*Trichs* (imm)
				Arithmetic Efficacies	
2	Example 4	10	9	>99.9%	>99.9%
				Geometric Efficacies	
2	Example 4	10	9	>99.9%	N/A

[a] Trichostrongyle species; [d] imm = immature;

Table 10: Larval differentiation results following group bulk coproculture- Larvae as a % of the total number counted

		Species Percentage				
Day	Treatment	*Haemonchus* spp.	*Trichostrongylus*[b] spp.	*Cooperia* spp.	*Ostertagia* spp.	Number of Larvae Counted
Day -3	All groups	93	7	0	0	100
Day 0	All groups	92	8	0	0	100
Day 10	Control	98	2	0	0	100
	Example 4	0	1	0	0	1

Conclusion: Excellent control (>99.9% reduction) of a mixed gastrointestinal strongyle burden as assessed by geometric faecal egg counts was achieved by the use of the Example 4 formulation at the conclusion of the trial (Day 10),.

Excellent control (>99.9% reduction) was achieved by the Example 4 formulation against the major nematodes, macrocyclic lactone and closantel resistant strains of *Haemonchus spp.* (adult and immature stages - geometric means), macrocyclic and albendazole resistant strains *Ostertagia spp.* (adult, immature and L4 stages - geometric means) and levamisole hydrochloride and albendazole resistant strains of *Trichostrongylus spp* (adult and immature stages – geometric means) as assessed by geometric total worm counts.

Trial JUA1240r: A property faecal egg count reduction study evaluating the therapeutic efficacy of the Example 4 formulation against field strains of mixed nematode population of either Haemonchus contortus, Trichostrongylus colubriformis and/or Teladorsagia circumcincta in sheep.

This study was conducted from the 16th May 2002 to the 20th August 2002 with the animal phase1 conducted between the 1st July 2002 to the 17th July 2002 and animal phase 2 between 5th September 2002 to the 4th October 2002. A trial site was sought, containing a mob of Merino sheep that were known to be harbouring resistant strains of nematodes (including either closantel resistant and/or macrocyclic lactone resistant *Haemonchus* species, as well as either benzimidazole resistant and/or levamisole resistant *Trichostrongylus colubriformis* and/or *Teladorsagia circumcincta*.) Pre-trial monitoring of the site confirmed that the intended trial animals carried a nematode burden of greater than 400 eggs/gram. A group coproculture was performed on these prospective trial sheep to establish the genera present.

On Day -3 of the trial, a mob of approximately 300 Merino ewes was mustered into a set of sheep yards. Eighty ewes were identified with uniquely numbered eartags and faecal sampled as they presented in the race. The faecal samples were returned to Veterinary Health Research for individual faecal egg counts and a bulk coproculture.

The sixty animals with the highest strongyle faecal egg counts, as determined by the Day -3 faecal egg counts, were selected for inclusion in the trial. These sheep were allocated to one (1) of six (6) treatment groups, on the basis of their faecal egg counts, such that each group had a similar arithmetic group mean faecal egg count.

On Day 0 (treatment day), each animal was weighed and treated according to the treatment schedule outlined in Table 11. Clinical observations were conducted one hour post-treatment to determine whether any adverse reactions had occurred in relation to treatments. None were detected.

Table 11: Treatment table (phase 1)

Treatment Group	Formulation	Dosage regimen	Number of sheep
1	Untreated control	-	10
2	Example 4	1 mL/5 kg	10
3	Ivomec (Liquid for Sheep, Merial Pty Ltd)	1 mL/4 kg	10
4	Sustain (Dover Laboratories Pty Ltd)	1 mL/5 kg	10
5	Youngs Levamisole (Youngs Animal Health Pty Ltd)	1 mL/4 kg	10
6	Valbazen (Coopers Animal Health)	1 mL/4 kg	10

The trial concluded on Day 13 when faecal samples were collected and returned to the Veterinary Health Research Laboratory for individual faecal egg counts and group coprocultures. The entire mob was administered an effective broad-spectrum anthelmintic to remove any existing worm burden.

The aim of this field study was to study and evaluate under field conditions, the therapeutic efficacy of Example 4 when administered to sheep that are known to be harbouring resistant strains of nematodes. The selected trial site was known to harbour closantel resistant *Haemonchus contortus*. This however was not confirmed during the initial phase of the study as a full dose of closantel was administered (as stated in the

protocol). Standard industry practice for diagnosis of closantel resistance in the field involves either the administration of a full dose of closantel and sequential sampling of treated sheep over three to six weeks post treatment, or alternatively administration of a 1/3 dose and sampling at 10 to14 days post treatment.

A second faecal egg count reduction study was conducted after consultation with the Study Sponsor to confirm the closantel resistance status at the trial site, "Kelvin East". The second phase of the study involved two groups of sheep each consisting of ten animals. Ten random faecal samples were collected prior to treatment from the mob of wethers to confirm a nematode burden of greater than 400 eggs/gram, and a group coproculture that confirmed a very high percentage (91%) of *Haemonchus contortus* were present. On Treatment Day (Day 0), individual faecal samples were collected from twenty animals as they presented in the race. These animals were weighed and weights recorded and treatments administered in accordance to the treatment regime (detailed in Table 12). Faecal samples were returned to Veterinary Health Research for individual faecal egg counts and group coprocultures. Animals were observed post treatment for adverse reactions. None were detected.

Table 12: Treatment table (phase 2)

Treatment Group	Formulation	Dosage Regimen	Number of Sheep
1	Untreated control	-	10
2	Sustain (Dover Laboratories Pty Ltd)	1 mL/15 kg	10

The second phase of this trial concluded on Day 11, with the collection of individual faecal samples from all animals. These samples were returned to Veterinary Health Research for individual faecal egg counts and group coprocultures.

Faecal samples for phase 1 were collected during pre trial monitoring, (Day -3), at treatment (Day 0) and at the conclusion of the trial (Day 13) and for phase 2 at treatment (Day 0) and at the conclusion of the trial (Day 11). Results from faecal egg counts, larval differentiation and calculated treatment efficacies are summarised in the accompanying tables 13-24 and figures 5 and 6. Note that in figures 5 and 6, "Jurox" refers to example 4.

Table 13: Pre trial monitoring results.

Date	Group mean faecal egg count (epg)	Range of faecal egg counts (epg)
01 July 2002 (Day -3)	900	320-1880

Table 14: Group arithmetic mean faecal egg counts and body weights at Day 0.

Group	Treatment	Group mean faecal egg count (epg)	Group mean body weight (kg)
1	Untreated control	984[1]	49.30[1]
2	Example 4	584[1]	45.25[1]
3	Ivomec	588[1]	46.05[1]
3	Sustain	584[1]	46.05[1]
5	Levamisole	452[1]	46.35[1]
6	Valbazen	328[1]	48.25[1]

[1] Means in the same column with different superscripts are significantly different at $p<0.05$

Table 15: Group arithmetic and geometric mean faecal egg counts (epg).

Group	Treatment	Pre-trial (Day -3)	Day 0	Day 13
Arithmetic Means				
1	Untreated controls	892	984[1]	664[1]
2	Example 4	872	584[1]	4[4]
3	Ivomec	940	588[1]	0[4]
4	Sustain	924	584[1]	160[1,2]
5	Levamisole	900	452[1]	12[3,4]
6	Valbazen	872	328[1]	68[2,3]

Geometric Means				
1	Untreated controls	823.0	691.5	340.3
2	Example 4	768.9	508.7	0.5
3	Ivomec	869.9	416.4	0
4	Sustain	860.1	450.1	97.4
5	Levamisole	834.1	379.7	2.1
6	Valbazen	818.9	179.7	14.9

[1] Means in the same column with different superscripts are significantly different at $p<0.05$

Table 16: Overall percentage efficacy calculated using arithmetic and geometric group mean faecal egg counts.

Group	Treatment	Efficacy (%)
Arithmetic Efficacy		
2	Example 4	99.4
3	Ivomec	>99.9
4	Sustain	75.9
5	Levamisole	98.19
6	Valbazen	89.76
Geometric Efficacy		
2	Example 4	99.87
3	Ivomec	>99.9
4	Sustain	71.37
5	Levamisole	99.4
6	Valbazen	95.61

Table 17: Percentages of nematode types present pre-trial, Day 0 and Day 13.

Day	Group	Treatment	*%Haem*	*%Trich*	*%Tel*	*%Coop*	*%Oes*	Total Larvae Counted
Pre-trial	All	-	94	5	-	-	1	100
Day 0	1	Untreated	93	5	2	-	-	100
	2	Example 4	83	5	8	2	2	100
	3	Ivomec	91	3	4	-	2	100
	4	Sustain	78	13	6	-	3	100
	5	Levamisole	91	4	2	1	2	100
	6	Valbazen	82	8	6	-	4	100
Day 13	1	Untreated	94	2	3	-	1	100
	2	Example 4	-	-	-	-	1	1
	3	Ivomec	-	-	-	-	-	nil
	4	Sustain	-	59	25	-	16	100
	5	Levamisole	-	88	12	-	-	100
	6	Valbazen	-	66	34	-	-	100

Haem - Haemonchus, Trich - Trichostrongylus, Tel - Teladorsagia, Coop - Cooperia, Oes - Oesophagostomum

Table 18: Efficacies calculated for each nematode genus.

Group	Treatment	*Haem*	*Trich*	*Tel*	*Coop*	*Oes*
2	Example 4	>99.9%	>99.9%	>99.9%	na	na
3	Ivomec	>99.9%	>99.9%	>99.9%	na	na
4	Sustain	>99.9%	-ve value	-ve value	na	na
5	Levamisole	>99.9%	20.48%	92.78%	na	na
6	Valbazen	>99.9%	-ve value	-ve value	na	na

Haem - Haemonchus, Trich - Trichostrongylus, Tel - Teladorsagia, Coop - Cooperia, Oes - Oesophagostomum

na – not assessed

Phase 2

Table 19: Treatment day monitoring results.

Date of Sampling	Group Mean Faecal Egg Count (eggs/gram)	Range of Faecal Egg Counts (eggs/gram)
23 Sept 2002 (Day 0)	1428	80-3000

Table 20: Group arithmetic mean faecal egg counts and body weights at Day 0.

Group	Treatment	Group Mean Faecal Egg Count (eggs/gram)	Group Mean Body Weight (kg)
1	Untreated controls	1628[1]	51.6[1]
2	Sustain	1228[1]	50.2[1]

[1] Means in the same column with different superscripts are significantly different at $p<0.05$

Table 21: Group arithmetic and geometric mean faecal egg counts.

Group	Treatment	Day 0	Day 11
Arithmetic Means			
1	Untreated controls	1628.0[1]	3008.0[1]
2	Sustain	1228.0[1]	2088.0[1]
Geometric Means			
1	Untreated controls	1237.7	2041.1
2	Sustain	940.0	1511.9

[1] Means in the same column with different superscripts are significantly different at $p<0.05$

Table 22: Overall percentage efficacy (arithmetic and geometric means)

Group	Treatment	Percentage Efficacy (%)
Arithmetic Efficacy		
2	1/3 Sustain	30.6
Geometric Efficacy		
2	1/3 Sustain	25.9

Table 23: Nematode population % – Pre-trial, Day 0 and Day 11 (based on faecal culture and larval differentiation).

Day	Group	Treatment	*%Haem*	*%Trich*	*%Tel*	*%Coop*	*%Oes*	Total counted
Pre-trial	All	-	91	7	-	-	2	100
Day 0	1	Untreated	95	3	1	-	1	100
	2	1/3 Sustain	87	7	2	-	4	100
Day 13	1	Untreated	93	6	1	-	-	100
	2	1/3 Sustain	92	4	3	-	1	100

Haem - Haemonchus, Trich - Trichostrongylus, Tel - Teladorsagia, Coop - Cooperia, Oes - Oesophagostomum

Table 24: Individual nematode efficacies.

Group	Treatment	*Haem*	*Trich*	*Tel*	*Coop*	*Oes*
2	1/3 Sustain	31.3%	53.7%	-ve value	na	na

Haem - Haemonchus, Trich - Trichostrongylus, Tel - Teladorsagia, Coop – Cooperia, Oes – Oesophagostomum

na – not assessed

-ve – negative

Conclusion: The second faecal egg count reduction test was to confirm the presence closantel resistant *Haemonchus* at the trial site. This was achieved by administering a one third dose of closantel to a group of ten (10) animals and the addition of another group of ten (10) animals retained as untreated controls. The use of a one third dose of closantel is standard industry practice for diagnosis of closantel resistance in the field. Reduced efficacy of closantel was observed against *Haemonchus*, confirming. The presence of closantel resistant *Haemonchus* at the trial site.

The inclusion of the levamisole and benzimidazole groups confirmed the resistance status of *Trichostrongylus*.

Excellent efficacy (> 99.0%) was attained by the Example 4 formulation against a mixed gastrointestinal population including closantel resistant *Haemonchus* as well as levamisole and benzimidazole resistant *Trichostrongylus*.

Trial JUA1273r: A property faecal egg count reduction study evaluating the therapeutic efficacy of the Example 4 formulation against field strains of mixed nematode populations, including closantel resistant strains of *Haemonchus contortus* in sheep.

This study was conducted from the 5th of September 2002 to the 23rd of October 2002, with the animal phase conducted between 10th of September 2002 and the 1st of October 2002. Routine monitoring of a trial site known to harbour closantel resistant strains of *Haemonchus contortus* was conducted to identify a suitably infected group of sheep. Pre-trial monitoring confirmed that one group of sheep (270 Merino hoggets) was suitably infected with a high burden of *Haemonchus contortus*.

On Day –2 of the trial individual faecal samples were collected from ninety (90) potential trial sheep and individual strongyle faecal egg counts performed. Trial sheep had already been identified using uniquely numbered ear tags as part of standard farming practice at the trial site. From the ninety (90) potential trial sheep sixty (60) sheep were selected and allocated (according to individual strongyle faecal egg counts) to six (6) groups of ten (10) sheep each, such that each group had a similar group arithmetic mean strongyle faecal egg count and range of faecal egg counts within the group.

On Day 0 of the trial (18th September 2002) selected trial sheep were weighed (see figure 7 for arithmetic mean body weights and note that the treatment "Jurox" refers to the treatment with Example 4), the weights recorded and individual faecal samples collected for individual strongyle faecal egg counts. Trial sheep in Group 2 were treated according to individual body weight with the test formulation, trial sheep in Groups 3-6 were treated with the respective reference formulation and trial sheep in Group 1 were retained untreated as negative controls. Groups 2, 3, 5 and 6 were treated at the recommended dose rate for each active, while sheep in Group 4 were treated at one third the normal closantel dose rate, to determine and demonstrate the presence of closantel resistance (Reference: Rolfe PF; *Fourth International Congress for Sheep Veterinartans* 1997, pg 55). Sheep were observed in the immediate post-treatment period for adverse reactions (none were observed). Individual strongyle faecal egg counts and group bulk coprocultures for larval differentiation were subsequently performed on the samples collected.

Trial sheep were returned to the sheep yards on Day 13 of the trial (1st October 2002) and individual faecal samples again collected. All trial sheep received a single therapeutic dose of Rycozole®[1] due to animal welfare concerns. Individual strongyle faecal egg counts and group bulk coprocultures for larval differentiation were subsequently performed on the samples collected.

Treatment efficacies were then calculated using group arithmetic and geometric strongyle faecal egg counts for the major strongyle species present (see figures 8 and 9 and note that the treatment "Jurox" refers to treatment with Example 4).

[1] Rycozole Oral Anthelmintic for Sheep and Cattle, Novartis Animal Health Australasia Pty Ltd

Table 25: Treatment table.

Group	Number of Sheep	Treatment	Active Constituent	Batch No.	Dose Volume (mL/kg)	Dose Rate
1	10	Untreated	---	---	---	---
2	10	Example 4	closantel 37.5 mg/mL, abamectin 1.0 mg/mL, albendazole 25 g/L, levamisole hydrochloride 40 mg/mL	FS489	1 mL/5 kg	closantel 7.5 mg/kg, abamectin 0.2 mg/kg, albendazole 5.0 mg/kg, levamisole hydrochloride 8 mg/kg
3	10	Ivomec®	ivermectin 0.8 mg/mL	51983	1 mL/4 kg	ivermectin 0.2 mg/kg
4	10	1/3 Sustain®	closantel 37.5 mg/mL	13146	1 mL/15 kg	closantel 2.5 mg/kg
5	10	Levamisole®	levamisole hydrochloride 32 mg/mL	6053	1 mL/4 kg	levamisole hydrochloride 8 mg/kg
6	10	Valbazen®	albendazole 19 mg/mL	V03790/2	1 mL/4 kg	albendazole 4.75 mg/kg

Table 26: Group arithmetic mean, maximum and minimum strongyle faecal egg counts and standard deviations following allocation.

Group	Treatment	Faecal Egg Count Day -2 (eggs/gram)	Maximum Faecal Egg Count Day -2 (eggs/gram)	Minimum Faecal Egg Count Day -2 (eggs/gram)	Standard Deviation Day -2
1	Untreated	1404.0	2760	640	635.7
2	Example 4	1432.0	2840	480	765.4
3	Ivomec®	1408.0	2600	640	682.9
4	1/3 Sustain®	1436.0	2840	600	693.7
5	Levamisole®	1516.4	2800	640	673.3
6	Valbazen®	1257.8	2680	520	737.1

Table 27: Treatment details.

Group	Treatment	Batch No.	Weight Day 0 (kg)	Dose Volume (mL/kg)	Mean Calculated Dose (mL)	Mean Administered Dose (mL)	Mean Administered Dose Volume (mL/x kg)
1	Untreated	---	26.5[1]	---	---	---	---
2	Example 4	FS489	24.9[1]	1 mL/5 kg	5.0	5.0	4.94
3	Ivomec®	51983	24.6[1]	1 mL/4 kg	5.9	6.0	4.11
4	1/3 Sustain®	13146	24.1[1]	1 mL/15 kg	1.6	1.7	14.15
5	Levamisole®	6053	23.0[1]	1 mL/4 kg	5.7	5.8	3.94
6	Valbazen®	V03790/2	26.0[1]	1 mL/4 kg	6.5	6.6	3.93

[1] Means within the same column with the same superscript are not significantly different at $p<0.05$

Faecal samples were collected during pre trial monitoring, on Day –2 for allocation purposes, at treatment (Day 0) and at the conclusion of the trial (Day 13). Results from faecal egg counts, larval differentiation and calculated treatment efficacies are summarised in the accompanying tables.

Table 28: Pre trial monitoring results

Date of Sampling	Group Mean Faecal Egg Count (eggs/gram)	Range of Faecal Egg Counts (eggs/gram)
10 September 2002	1732	1000 - 2360

Table 29: Group Arithmetic and Geometric Mean strongyle faecal egg counts during the trial (excluding *Nematodirus* spp.)

Group	Treatment	Batch No.	Faecal Egg Count (Pre-Trial)	Faecal Egg Count (Day 0)	Faecal Egg Count (Day 13)
	Arithmetic Means				
1	Untreated	---	1404.0[1]	896.0[1]	1360.0[1]
2	Example 4	FS489	1432.0[1]	1536.0[1]	0.0[3]
3	Ivomec®	51983	1408.0[1]	1506.7[1]	60.0[23]
4	1/3 Sustain®	13146	1436.0[1]	1336.0[1]	236.0[12]
5	Levamisole ®	6053	1400.0[1]	1784.0[1]	4.0[3]
6	Valbazen®	V03790/2	1400.0[1]	1240.0[1]	204.0[12]
	Geometric Means				
1	Untreated	---	1285.0[1]	777.5[1]	1130.7[1]
2	Example 4	FS489	1253.7[1]	1365.0[1]	0.0[3]
3	Ivomec®	51983	1180.6[1]	1065.0[1]	31.8[23]
4	1/3 Sustain®	13146	1390.7[1]	1371.7[1]	152.5[12]
5	Levamisole ®	6053	1263.0[1]	1483.8[1]	0.4[3]
6	Valbazen®	V03790/2	1233.3[1]	1073.7[1]	176.1[12]

[1,2,3] *Means within the same column with the same superscript are not significantly different at* $p<0.05$

Table 30: Larval differentiation results from group bulk coprocultures.

Date	Day	Group	Treatment	*Haem*[a]. spp.	Trich[b]. spp.	*Telodorsagia* spp.	*Coop*[c]. spp.	*Oesoph*[d]. spp.	Total Larvae Counted
10-Sep-02	-9	All	---	100%	0	0	0	0	100
		1	Untreated	100%	0%	0%	0%	0%	100
		2	Example 4	100%	0%	0%	0%	0%	100
19-Sep-02	0	3	Ivomec®	99%	1%	0%	0%	0%	100
		4	1/3 Sustain®	100%	0%	0%	0%	0%	100
		5	Levamisole®	100%	0%	0%	0%	0%	100
		6	Valbazen®	100%	0%	0%	0%	0%	100
		1	Untreated	100%	0%	0%	0%	0%	100
		2	Example 4	0%	0%	0%	0%	0%	100
01-Oct-02	13	3	Ivomec®	89%	3%	0%	8%	0%	100
		4	1/3 Sustain®	98%	0%	0%	2%	0%	100
		5	Levamisole®	53%	48%	0%	0%	0%	40
		6	Valbazen®	97%	3%	0%	0%	0%	100

[a] *Haemonchus* spp., [b]Trichostrongylus spp., [c]*Cooperia* spp., [d]*Oesophagostomum* spp.

Table 31: Overall treatment efficacies, against all strongyle species (apart from *Nematodirus* spp.)

Group	Treatment	Batch No.	Efficacy at Day 13
Arithmetic Means			
2	Example 4	FS489	>99.9%
3	Ivomec®	51983	95.6%
4	1/3 Sustain®	13146	82.6%
5	Levamisole®	6053	99.7%
6	Valbazen®	V03790/2	85.0%
Geometric Means			
2	Example 4	FS489	>99.9%
3	Ivomec®	51983	97.2%
4	1/3 Sustain®	13146	97.2%
5	Levamisole®	6053	>99.9%
6	Valbazen®	V03790/2	84.4%

Table 32: Treatment efficacies against *Haemonchus contortus.*

Group	Treatment	Batch No.	Efficacy at Day 13
Arithmetic Means			
2	Example 4	FS489	>99.9%
3	Ivomec®	51983	96.1%
4	1/3 Sustain®	13146	83.0%
5	Levamisole®	6053	99.8%
6	Valbazen®	V03790/2	85.5%
Geometric Means			
2	Example 4	FS489	>99.9%
3	Ivomec®	51983	97.5%
4	1/3 Sustain®	13146	86.8%
5	Levamisole®	6053	>99.9%
6	Valbazen®	V03790/2	84.9%

Conclusion: Excellent efficacy (greater than 99.9% based on group arithmetic and geometric means and larval differentiation results) was attained by the Example 4 formulation against a gastrointestinal strongyle population consisting almost exclusively of *Haemonchus contortus*.

Efficacies attained by the comparison formulations against this strain of *Haemonchus contortus* ranged from 85.5% for the albendazole formulation (Valbazen®) through 96.1% for the ivermectin formulation (Ivomec®) to 99.8% for the levamisole formulation (Levamisole®), based on group arithmetic mean faecal egg counts and larval differentiation. Efficacies attained against this strain based on geometric mean faecal egg counts and larval differentiation were 84.9%, 97.5% and >99.9% for these formulations respectively. These results indicate that this strain is moderately resistant to white drenches (benzimidazoles) and fully susceptible to levamisoles, with a slight but non-significant reduction in efficacy for ivermectin. Ivermectin was 96.1% (arithmetic) and 97.5% (geometric) efficacious, which establishes that this strain could not be defined as macrocyclic lactone resistant at present.

Treatment with a 1/3 dose of closantel resulted in a treatment efficacy of 83.0% based on arithmetic group mean faecal egg counts and a treatment efficacy of 86.8% based on geometric group mean faecal egg counts, confirming the presence of moderate closantel resistance by this *Haemonchus* strain. Insufficient numbers of other gastrointestinal strongyles (*Nematodirus*, *Teolodorsagia* and Trichostrongylus species) were present to draw any conclusions about efficacy of the test formulation against these strains.

Trial JUA1270r: A property faecal egg count reduction study evaluating the therapeutic efficacy of the Example 4 formulation against field strains of mixed nematode populations, including macrocyclic lactone resistant strains of *Haemonchus contortus* in sheep in sheep.

This study was conducted from the 5th of September 2002 to the 7th of November 2002, with the animal phase conducted between 11th and 25th of October 2002. Routine monitoring of a trial site known to harbour macrocyclic lactone resistant strains of *Haemonchus contortus* was conducted to identify a suitably infected group of sheep. Pre-trial monitoring confirmed that one group of sheep (approximately 200 Merino wether hoggets) was suitably infected with a high burden of *Haemonchus contortus.*

On Day 0 of the trial, ninety six (96) sheep were randomly selected from a larger mob as they appeared in the sheep handling facility, weighed (see figure 10 for arithmetic mean body weights and note that the treatment "Jurox" refers to treatment with example 4) and individual faecal samples collected for subsequent individual strongyle faecal egg counts and group bulk coprocultures. Sheep had been previously allocated to six (6) treatment groups, one (1) of eleven (11) sheep to act as untreated (negative) controls and five (5) groups of seventeen (17) sheep, to be treated with the test formulation and a range of registered reference formulations. Trial sheep in Group 1 were retained untreated, while sheep in Groups 2-6 were treated according to individual body weight with the test and reference formulations. Sheep were observed in the immediate post-treatment period for adverse reactions (none were observed). Trial sheep were then returned to their parent flock and maintained in open grazing paddocks.

On Day 13 of the trial sheep were returned to the sheep handling facilities. Individual faecal samples were collected from trial sheep and individual strongyle faecal egg counts and group bulk coprocultures for larval differentiation were subsequently performed on the samples collected.

Treatment efficacies were then calculated using group arithmetic and geometric strongyle faecal egg counts for the major strongyle species present (see figures 11 and 12 and note that the treatment "Jurox" refers to treatment with Example 4).

Table 33: Treatment table.

Group	Number of Sheep	Treatment	Active Constituent	Batch No.	Dose Volume (mL/kg)	Dose Rate
1	11	Untreated	---	---	---	---
2	17	Example 4	closantel 37.5 mg/mL, abamectin 1.0 mg/mL, albendazole 25 g/L, levamisole hydrochloride 40 mg/mL	RD0006	1 mL/5 kg	closantel 7.5 mg/kg, abamectin 0.2 mg/kg, albendazole 5.0 mg/kg, levamisole hydrochloride 8 mg/kg
3	17	Ivomec®	ivermectin 0.8 mg/mL	51983	1 mL/4 kg	ivermectin 0.2 mg/kg
4	17	Sustain®	closantel 37.5 mg/mL	13146	1 mL/15 kg	closantel 2.5 mg/kg
5	17	Levamisole Gold®	levamisole hydrochloride 32 mg/mL	7895V2	1 mL/4 kg	levamisole hydrochloride 8 mg/kg
6	17	Valbazen®	albendazole 19 mg/mL	V03790/2	1 mL/4 kg	albendazole 4.75 mg/kg

Table 34: Group arithmetic mean, maximum and minimum strongyle faecal egg counts and standard deviations following allocation.

Group	Treatment	Mean Faecal Egg Count Day 0 (eggs/gram)	Maximum Faecal Egg Count Day 0 (eggs/gram)	Minimum Faecal Egg Count Day 0 (eggs/gram)	Standard Deviation Day 0 FEC
1	Untreated	600.0[1]	1760.0	40.0	491.2
2	Example 4	690.0[1]	2320.0	0.0	640.6
3	Ivomec®	1068.2[1]	4280.0	200.0	1045.7
4	Sustain®	816.5[1]	2000.0	0.0	681.9
5	Levamisole Gold®	708.2[1]	2840.0	0.0	744.8
6	Valbazen®	668.2[1]	1480.0	0.0	553.5

Table 35: Treatment details.

Group	Treatment	Batch No.	Weight Day 0 (kg)	Dose Volume (mL/kg)	Mean Calculated Dose (mL)	Mean Administered Dose (mL)	Mean Administered Dose Volume (1 mL/x kg)
1	Untreated	---	30.0[1]	---	---	---	---
2	Example 4	RD0006	28.8[1]	1 mL/5 kg	5.76	5.8	4.97
3	Ivomec®	51983	28.5[1]	1 mL/4 kg	7.13	7.2	3.96
4	Sustain®	13146	29.2[1]	1 mL/5 kg	5.84	5.9	4.95
5	Levamisole Gold®	7895V2	28.8[1]	1 mL/4 kg	7.19	7.3	3.96
6	Valbazen®	V03790/2	29.5[1]	1 mL/4 kg	7.38	7.5	3.96

[1] Means within the same column with the same superscript are not significantly different at $p<0.05$

Table 36: Pre trial monitoring results

Date of Sampling	Group Mean Faecal Egg Count (eggs/gram)	Range of Faecal Egg Counts (eggs/gram)
10 September 2002	408	40-760

Table 37: Group Arithmetic and Geometric Mean strongyle faecal egg counts during the trial.

Group	Treatment	Batch No.	Faecal Egg Count (Day 0)	Faecal Egg Count (Day 14)
	Arithmetic Means			
1	Untreated	---	600.0[1]	1043.6[1,2]
2	Example 4	RD0006	690.0[1]	137.5[3]
3	Ivomec®	51983	1068.2[1]	1421.2[1]
4	Sustain®	13146	816.5[1]	710.6[1,2,3]
5	Levamisole Gold®	7895V2	708.2[1]	344.0[2,3]
6	Valbazen®	V03790/2	668.2[1]	875.0[1,2]
	Geometric Means			
1	Untreated	---	376.1[1]	673.0[1,2]
2	Example 4	RD0006	361.5[1]	29.2[3]
3	Ivomec®	51983	751.3[1]	918.0[1]
4	Sustain®	13146	410.1[1]	233.7[1,2,3]
5	Levamisole Gold®	7895V2	330.8[1]	141.7[2,3]
6	Valbazen®	V03790/2	243.2[1]	652.7[1,2]

[1,2,3] Means within the same column with the same superscript are not significantly different at $p<0.05$

Table 38: Larval differentiation results from group bulk coprocultures.

Date	Day	Group	Treatment	*Haem*[a]. spp.	Trich[b]. spp.	*Telodorsagia* spp.	*Coop*[c]. spp.	*Oesoph*[d]. spp.	Total Larvae Counted
4-Oct-02	-7	All	---	100%	0	0	0	0	100
11-Oct-02	0	1	Untreated	100%	0%	0%	0%	0%	100
		2	Example 4	100%	0%	0%	0%	0%	100
		3	Ivomec®	100%	0%	0%	0%	0%	100
		4	Sustain®	100%	0%	0%	0%	0%	100
		5	Levamisole Gold®	100%	0%	0%	0%	0%	100
		6	Valbazen®	100%	0%	0%	0%	0%	100
25-Oct-02	14	1	Untreated	100%	0	0	0	0	100
		2	Example 4	100%	0	0	0	0	6
		3	Ivomec®	100%	0	0	0	0	100
		4	Sustain®	100%	0	0	0	0	100
		5	Levamisole Gold®	100%	0	0	0	0	100
		6	Valbazen®	100%	0	0	0	0	100

[a] *Haemonchus* spp., [b]Trichostrongylus spp., [c]*Cooperia* spp., [d]*Oesophagostomum* spp.

Table 39: Treatment efficacies against *Haemonchus contortus*.

Group	Treatment	Batch No.	Efficacy at Day 14
Arithmetic Means			
2	Example 4	RD0006	86.8%
3	Ivomec®	51983	Negative Efficacy
4	Sustain®	13146	31.9%
5	Levamisole Gold®	7895V2	67.0%
6	Valbazen®	V03790/2	16.2%
Geometric Means			
2	Example 4	RD0006	95.7%
3	Ivomec®	51983	Negative Efficacy
4	Sustain®	13146	65.3%
5	Levamisole Gold®	7895V2	78.9%
6	Valbazen®	V03790/2	3.0%

Conclusion: Efficacies attained by the formulations against this strain of *Haemonchus contortus* for the ivermectin formulation (Ivomec®), the albendazole formulation (Valbazen®), the closantel formulation (full dose Sustain®), the levamisole formulation (Levamisole Gold®) and for the test formulation, based on group geometric mean faecal egg counts and larval differentiation were negative, 3.0%, 65.3%, 78.9% and >95% respectively.

While moderate efficacies were attained by the reference closantel formulation, a full (label) dose rate of this formulation was used in this case. In instances of moderate closantel resistance efficacies are still usually >95% for a full dose, with a reduction in initial efficacy only evident at a 1/3 normal dose rate. This particular strain is therefore severely resistant to closantel. These results indicate that this strain also has severe resistance to white drenches (benzimidazoles) and macrocyclic lactones and moderate resistance to levamisole. This strain of *Haemonchus contortus* is, therefore, moderately to severely resistant to all four drug families. Unexpectedly, the Example 4 formulation containing an example of all four of these families resulted in effective treatment of the infestation.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

CLAIMS:-

1. A synergistic anthelmintically effective composition consisting of at least one compound selected from each of the following groups:

macrocylic lactones; benzimidazoles; salicylanilides; and imidazothiazoles; and a therapeutically acceptable carrier.

2. The composition of claim 1 wherein the macrocyclic lactone compound is at least one selected from the group consisting of abamectin, ivermectin, doramectin, moxidectin, cydectin and milbenycin.

3. The composition of claim 1 wherein the benzimidazole compound is at least one selected from the group consisting of albendazole, fenbendazole, thiabendazole, oxfenbendazole, fenbantel, mebendazole, parbendazole, flubendazole, oxibendazole and carbendazole.

4. The composition of claim 1 wherein the salicylanilide compound is at least one selected from the group consisting of closantel and niclosamide.

5. The composition of claim 1 wherein the imidazothiazole compound is at least one selected from the group consisting of levamisole, pyrantel pamoate and butamisole.

6. The composition of claim 2 wherein:

the selected macrocyclic lactone compound is at least abamectin;

the benzimidazole compound is at least one selected from the group consisting of albendazole, fenbendazole, thiabendazole, oxfenbendazole, fenbantel, mebendazole, parbendazole, flubendazole, oxibendazole and carbendazole;

the salicylanilide compound is at least one selected from the group consisting of closantel and niclosamide; and

the imidazothiazole compound is at least one selected from the group consisting of levamisole, pyrantel pamoate and butamisole.

7. The composition of claim 3 wherein:

the benzimidazole compound is at least albendazole;

the macrocyclic lactone compound is at least one selected from the group consisting of abamectin, ivermectin, doramectin, moxidectin, cydectin and milbenycin;

the salicylanilide compound is at least one selected from the group consisting of closantel and niclosamide; and

the imidazothiazole compound is at least one selected from the group consisting of levamisole, pyrantel pamoate and butamisole.

8. The composition of claim 4 wherein:

the salicylanilide compound is at least closantel;

the macrocyclic lactone compound is at least one selected from the group consisting of abamectin, ivermectin, doramectin, moxidectin, cydectin and milbenycin;

the benzimidazole compound is at least one selected from the group consisting of albendazole, fenbendazole, thiabendazole, oxfenbendazole, fenbantel, mebendazole, parbendazole, flubendazole, oxibendazole and carbendazole; and

the imidazothiazole compound is at least one selected from the group consisting of levamisole, pyrantel pamoate and butamisole.

9. The composition of claim 5 wherein:

the imidazothiazole compound as at least levamisole;

the macrocyclic lactone compound is at least one selected from the group consisting of abamectin, ivermectin, doramectin, moxidectin, cydectin and milbenycin;

the benzimidazole compound is at least one selected from the group consisting of albendazole, fenbendazole, thiabendazole, oxfenbendazole, fenbantel, mebendazole, parbendazole, flubendazole, oxibendazole and carbendazole; and

the salicylanilide compound is at least one selected from the group consisting of closantel and niclosamide.

10. The composition of any one of claims 1 to 5 wherein the composition consists of at least abamectin, albendazole, closantel and levamisole.

11. The composition of claim 10 wherein the levamisole is included in the form of a water soluble salt.

12. The composition of claim 11 wherein the water soluble salt is a hydrochloride salt.

13. The composition of any one of claims 1 to 12 wherein the composition comprises:

macrocyclic lactone compounds in an amount of from 0.1-20.0 g/L;
benzimidazole compounds in an amount of from 1-100g/L;
salicylanilide compounds in an amount of from 1-100 g/L; and
imidazothiazole compounds in an amount of from 1-100 g/L.

14. The composition of any one of claims 1 to 12 wherein the composition comprises:

macrocyclic lactone compounds in an amount of from 0.5- 1.5 g/L;
benzimidazole compounds in an amount of from 18-30 g/L;
salicylanilide compounds in an amount of from 30-50 g/L; and
imidazothiazole compounds in an amount of from 30-50 g/L.

15. The composition of any one of claims 1 to 14 wherein the composition is in the form of a drench, a pour-on transdermal formulation, a slow release bolus or an injectable formulation.

16. The composition of any one of claims 1 to 14 wherein the composition is in the form of a drench including a solvent system for the macrocylic lactones, one or more dispersing and suspending agents for the benzimidazoles and salicylanilides, one or more surfactants, one or more preservatives, a buffering system and water as a carrier.

17. The composition of claim 16 wherein the solvent system for the macrocyclic lactones includes at least one solvent selected from the group consisting of: polyethylene glycol, tetraglycol, ethanol, benzyl alcohol and propylene glycol.

18. The composition of claim 16 wherein the dispersing and suspending agents for the benzimidazoles and salicylanilides include at least one selected from the group consisting of: glyceryl palmitostearate, bentonite, colloidal silica, xanthan gum and polymeric pyrrolidones.

19. The composition of claim 16 wherein the surfactant is polysorbate 80 and/or ethoxylated castor oil.

20. The composition of claim 16 wherein the buffering system includes monobasic and dibasic sodium phosphate.

21. A method of treating parasitic infections in an animal comprising administering to the animal, a synergistic anthelmintically effective amount of a composition which consists of at least one compound selected from each of the following groups: macrocylic lactones; benzimidazoles; salicylanilides; and imidazothiazoles; and a therapeutically acceptable carrier.

22. The method of claim 21 wherein the macrocyclic lactone compound is at least one selected from the group consisting of abamectin, ivermectin, doramectin, moxidectin, cydectin and milbenycin.

23. The method of claim 21 wherein the benzimidazole compound is at least one selected from the group consisting of albendazole, fenbendazole, thiabendazole, oxfenbendazole, fenbantel, mebendazole, parbendazole, flubendazole, oxibendazole and carbendazole.

24. The method of claim 21 wherein the salicylanilide compound is at least one selected from the group consisting of closantel and niclosamide.

25. The method of claim 21 wherein the imidazothiazole compound is at least one selected from the group consisting of levamisole, pyrantel pamoate and butamisole.

26. The method of claim 22 wherein:

the selected macrocyclic lactone compound is at least abamectin;

the benzimidazole compound is at least one selected from the group consisting of albendazole, fenbendazole, thiabendazole, oxfenbendazole, fenbantel, mebendazole, parbendazole, flubendazole, oxibendazole and carbendazole;

the salicylanilide compound is at least one selected from the group consisting of closantel and niclosamide; and

the imidazothiazole compound is at least one selected from the group consisting of levamisole, pyrantel pamoate and butamisole.

27. The method of claim 23 wherein:

the benzimidazole compound is at least albendazole;

the macrocyclic lactone compound is at least one selected from the group consisting of abamectin, ivermectin, doramectin, moxidectin, cydectin and milbenycin;

the salicylanilide compound is at least one selected from the group consisting of closantel and niclosamide; and

the imidazothiazole compound is at least one selected from the group consisting of levamisole, pyrantel pamoate and butamisole.

28. The method of claim 24 wherein:

the salicylanilide compound is at least closantel;

the macrocyclic lactone compound is at least one selected from the group consisting of abamectin, ivermectin, doramectin, moxidectin, cydectin and milbenycin;

the benzimidazole compound is at least one selected from the group consisting of albendazole, fenbendazole, thiabendazole, oxfenbendazole, fenbantel, mebendazole, parbendazole, flubendazole, oxibendazole and carbendazole; and

the imidazothiazole compound is at least one selected from the group consisting of levamisole, pyrantel pamoate and butamisole.

29. The method of claim 25 wherein:

the imidazothiazole compound as at least levamisole;

the macrocyclic lactone compound is at least one selected from the group consisting of abamectin, ivermectin, doramectin, moxidectin, cydectin and milbenycin;

the benzimidazole compound is at least one selected from the group consisting of albendazole, fenbendazole, thiabendazole, oxfenbendazole, fenbantel, mebendazole, parbendazole, flubendazole, oxibendazole and carbendazole; and

the salicylanilide compound is at least one selected from the group consisting of closantel and niclosamide.

30. The method of any one of claims 21 to 25 wherein the composition consists of at least abamectin, albendazole, closantel and levamisole.

31. The method of claim 30 wherein the levamisole is included in the form of a water soluble salt.

32. The method of claim 31 wherein the water soluble salt is a hydrochloride salt.

33. The method of any one of claims 21 to 32 wherein the composition comprises:

macrocyclic lactone compounds in an amount of from 0.1-20.0 g/L;

benzimidazole compounds in an amount of from 1-100g/L;

salicylanilide compounds in an amount of from 1-100 g/L; and
imidazothiazole compounds in an amount of from 1-100 g/L.

34. The method of any one of claims 21 to 32 wherein the composition comprises:
macrocyclic lactone compounds in an amount of from 0.5- 1.5 g/L;
benzimidazole compounds in an amount of from 18-30 g/L;
salicylanilide compounds in an amount of from 30-50 g/L; and
imidazothiazole compounds in an amount of from 30-50 g/L.

35. The method of any one of claims 21 to 34 wherein the method is a method of treating infection in an animal by at least one species of parasite selected from the group consisting of *Haemonchus contortus*, *Haemonchus placei*, *Ostertagia circumcincta*, *Trichostrongylus axei*, *Trichostrongylus colubriformis*, *Trichostrongylus vitrinus*, *Cooperia curticel*, *Cooperia oncophera*, *Nematodirus spathiger*, *Nematodirus filicollis*, *Chabertia ovina*, *Oesophagostomum columbianum*, *Oesophagostomum venulosum*, *Trichuris ovis*, *Strongyloides papillosus*, *Bunostomum spp*, *Oestrus ovis*, *Dictyocaulus viviparus*, *Fasciola hepatica*, and *Monezia*.

36. The method of any one of claims 21 to 34 wherein the method is a method of treating infection in an animal by parasites resistant to at least one of each of the groups macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles.

37. The method of any one of claims 21 to 34 wherein the method is a method of treating infection in an animal by parasites resistant to at least two of each of the groups macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles.

38. The method of any one of claims 21 to 34 wherein the method is a method of treating infection in an animal by parasites resistant to at least three of each of the groups macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles.

39. The method of any one of claims 21 to 34 wherein the method is a method of treating infection in an animal by parasites resistant to all of the groups macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles.

40 The method of any one of claims 21 to 34 wherein the method is a method of treating infection in an animal by gastro-intestinal worms and liver fluke.

41. The method of any one of claims 21 to 40 wherein the composition is administered to an animal prior to introduction to a land area so as to prevent the land area from becoming infested with parasites which may or may not be resistant to one or more compounds selected from the groups consisting of macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles.

42. The use of a synergistic anthelmintically effective amount of a composition which consists of at least one compound selected from each of the following groups: macrocyclic lactones, benzimidazoles, salicylanilides and imidazothiazoles and a therapeutically acceptable carrier, in the treatment of a parasitic infection in an animal.

43. The use of claim 42 wherein the macrocyclic lactone compound is at least one selected from the group consisting of abamectin, ivermectin, doramectin, moxidectin, cydectin and milbenycin.

44. The use of claim 42 wherein the benzimidazole compound is at least one selected from the group consisting of albendazole, fenbendazole, thiabendazole, oxfenbendazole, fenbantel, mebendazole, parbendazole, flubendazole, oxibendazole and carbendazole.

45. The use of claim 42 wherein the salicylanilide compound is at least one selected from the group consisting of closantel and niclosamide.

46. The use of claim 42 wherein the imidazothiazole compound is at least one selected from the group consisting of levamisole, pyrantel pamoate and butamisole.

47. The use of claim 43 wherein:

the selected macrocyclic lactone compound is at least abamectin;

the benzimidazole compound is at least one selected from the group consisting of albendazole, fenbendazole, thiabendazole, oxfenbendazole, fenbantel, mebendazole, parbendazole, flubendazole, oxibendazole and carbendazole;

the salicylanilide compound is at least one selected from the group consisting of closantel and niclosamide; and

the imidazothiazole compound is at least one selected from the group consisting of levamisole, pyrantel pamoate and butamisole.

48. The use of claim 44 wherein:

the benzimidazole compound is at least albendazole;

the macrocyclic lactone compound is at least one selected from the group consisting of abamectin, ivermectin, doramectin, moxidectin, cydectin and milbenycin;

the salicylanilide compound is at least one selected from the group consisting of closantel and niclosamide; and

the imidazothiazole compound is at least one selected from the group consisting of levamisole, pyrantel pamoate and butamisole.

49. The use of claim 45 wherein:

the salicylanilide compound is at least closantel;

the macrocyclic lactone compound is at least one selected from the group consisting of abamectin, ivermectin, doramectin, moxidectin, cydectin and milbenycin;

the benzimidazole compound is at least one selected from the group consisting of albendazole, fenbendazole, thiabendazole, oxfenbendazole, fenbantel, mebendazole, parbendazole, flubendazole, oxibendazole and carbendazole; and

the imidazothiazole compound is at least one selected from the group consisting of levamisole, pyrantel pamoate and butamisole.

50. The use of claim 46 wherein:

the imidazothiazole compound as at least levamisole;

the macrocyclic lactone compound is at least one selected from the group consisting of abamectin, ivermectin, doramectin, moxidectin, cydectin and milbenycin;

the benzimidazole compound is at least one selected from the group consisting of albendazole, fenbendazole, thiabendazole, oxfenbendazole, fenbantel, mebendazole, parbendazole, flubendazole, oxibendazole and carbendazole; and

the salicylanilide compound is at least one selected from the group consisting of closantel and niclosamide.

51. The use of claim 42 wherein the composition consists of at least abamectin, albendazole, closantel and levamisole.

52. The use of claim 51 wherein the levamisole is included in the form of a water soluble salt.

53. The use of claim 52 wherein the water soluble salt is a hydrochloride salt.

54. The use of any one of claims 42 to 53 wherein the composition comprises:
macrocyclic lactone compounds in an amount of from 0.1-20.0 g/L;
benzimidazole compounds in an amount of from 1-100g/L;
salicylanilide compounds in an amount of from 1-100 g/L; and
imidazothiazole compounds in an amount of from 1-100 g/L.

55. The use of any one of claims 42 to 53 wherein the composition comprises:
macrocyclic lactone compounds in an amount of from 0.5- 1.5 g/L;
benzimidazole compounds in an amount of from 18-30 g/L;
salicylanilide compounds in an amount of from 30-50 g/L; and
imidazothiazole compounds in an amount of from 30-50 g/L.

56. The use of any one of claims 42 to 55 wherein the parasitic infection in the animal to be treated is infection by at least one species of parasite selected from the group consisting of *Haemonchus contortus, Haemonchus placei, Ostertagia circumcincta, Trichostrongylus axei, Trichostrongylus colubriformis, Trichostrongylus vitrinus, Cooperia curticel, Cooperia oncophera, Nematodirus spathiger, Nematodirus filicollis, Chabertia ovina, Oesophagostomum columbianum, Oesophagostomum venulosum, Trichuris ovis, Strongyloides papillosus, Bunostomum spp, Oestrus ovis, Dictyocaulus viviparus, Fasciola hepatica,* and *Monezia*.

57. The use of any one of claims 42 to 55 wherein the parasitic infection in the animal to be treated is infection by parasites resistant to at least one of each of the groups macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles.

58. The use of any one of claims 42 to 55 wherein the parasitic infection in the animal to be treated is infection by parasites resistant to at least two of each of the groups macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles.

59. The use of any one of claims 42 to 55 wherein the parasitic infection in the animal to be treated is infection by parasites resistant to at least three of each of the groups macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles.

60. The use of any one of claims 42 to 55 wherein the parasitic infection in the animal to be treated is infection by parasites resistant to all of the groups macrocylic lactones, benzimidazoles, salicylanilides and imidazothiazoles.

61 The use of any one of claims 42 to 55 wherein the parasitic infection in the animal to be treated is infection by gastro-intestinal worms and liver fluke.

62 The use of any one of claims 42 to 61 wherein the composition is used in the treatment of a parasitic infection in an animal selected from the group consisting of sheep, goats, ruminants and camelids.

Figure 1: Faecal Egg Counts (based on Arithmetic Means).

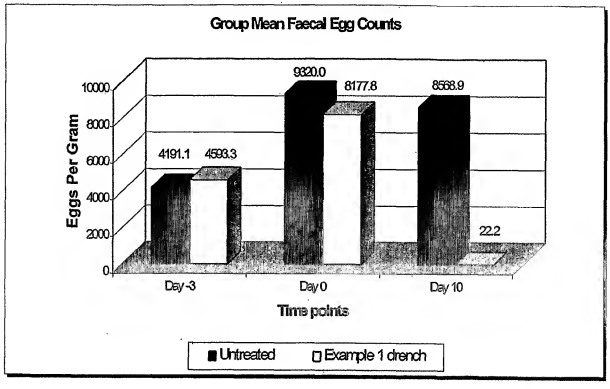


Figure 2: Percentage reduction of Strongyles (based on Geometric Means)

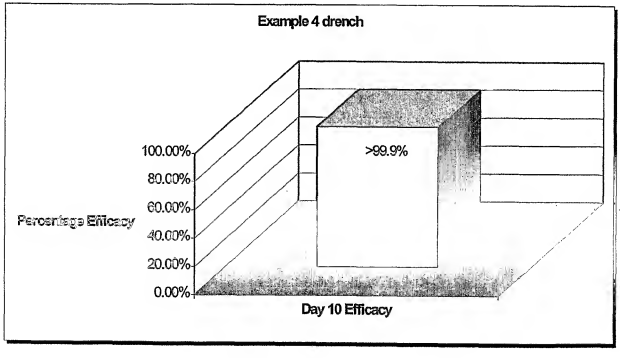
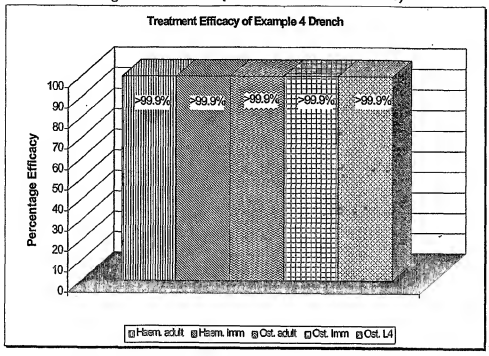
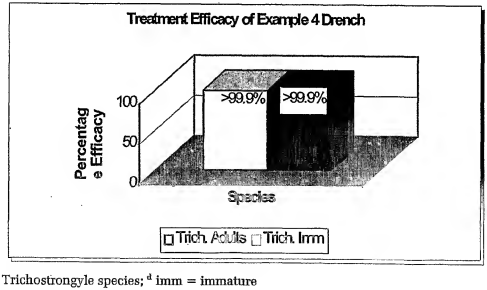


Figure 3: Percentage reduction of abomasal *Haemonchus contortus* and *Ostertagia circumcincta* (based on Geometric Means)



Note:
Haem. = Haemonchus species; Ost. = Ostertagia species; imm = immature; L4 = fourth larval stage

Figure 4: Percentage reduction of small intestinal *Trichostrongylus colubriformis* (based on Geometric Means)



Note: [a]
Trichostrongyle species; [d] imm = immature

Figure 5 Arithmetic group mean faecal egg counts pre-trial, Day 0 and Day 13

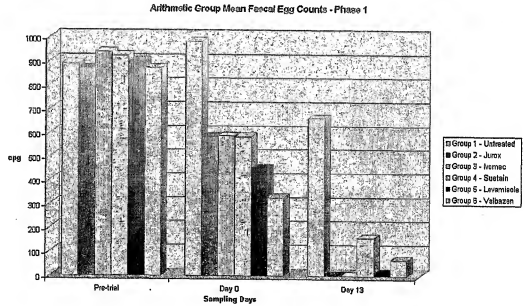


Figure 6: Arithmetic group mean faecal egg counts at Day 0 and Day 11.

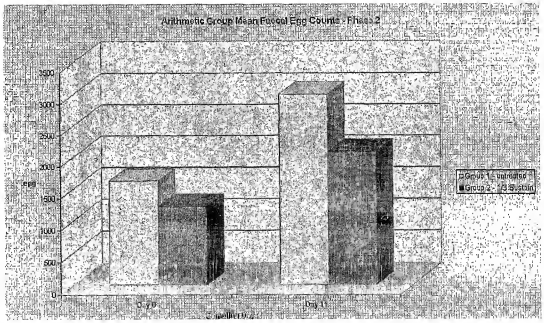


Figure 7: Group arithmetic mean body weights at treatment.

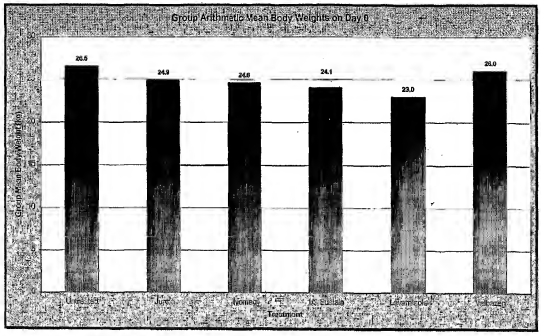


Figure 8: Treatment efficacies against *Haemonchus*, based on group arithmetic mean faecal egg counts.

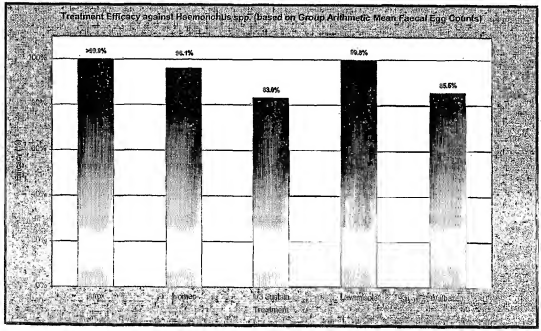


Figure 9: Treatment efficacies against *Haemonchus*, based on group geometric mean faecal egg counts.

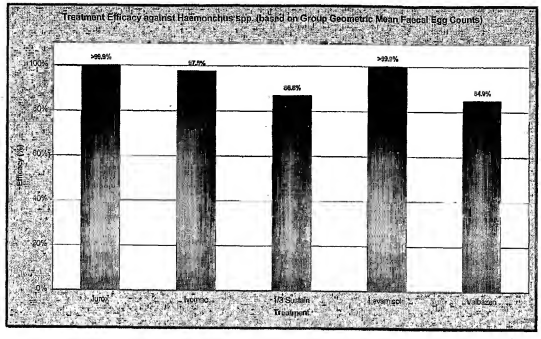


Figure 10: Group arithmetic mean body weights at treatment.

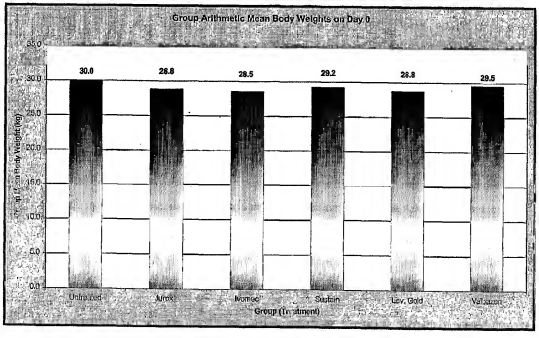


Figure 11: Treatment efficacies against *Haemonchus*, based on group arithmetic mean faecal egg counts.

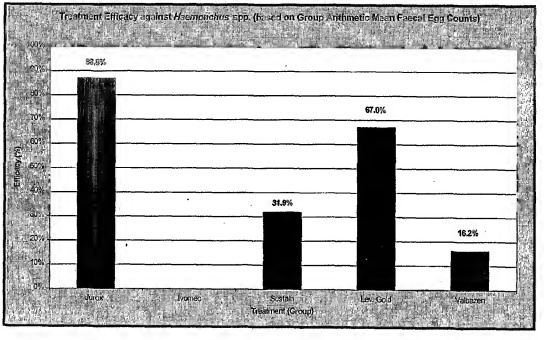
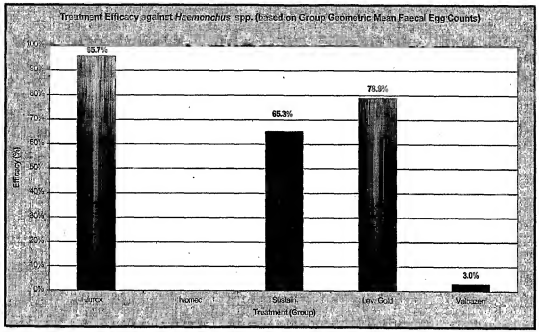


Figure 12: Treatment efficacies against *Haemonchus*, based on group geometric mean faecal egg counts.



INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2004/000126

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61K 31/277, 31/365, 31/4184, 31/429; A61P 33/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT and CAS. Keywords: abamectin, ivermectin, doramectin, moxidectin, cydectin, milbenycin, albendazole, fenbendazole, thiabendazole, oxfenbendazole, fenbantel, mebendazole, parbendazole, flubendazole, oxibendazole, carbendazole, closantel, niclosamide, levamisol, pyrantel pamoate, butamisole, fenbantel

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2001/060380 A1 (PHOENIX SCIENTIFIC, INC.) 23 August 2001 See the whole document	1-62
A	Louw J.P. et al. Jl. S. Afr. Vet. Ass. (1993) 64(2): 71-75 See the abstract	1-62

☐ Further documents are listed in the continuation of Box C

☒ See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 March 2004	24 MAR 2004
Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	S. Chew Telephone No : (02) 6283 2248

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU2004/000126

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	2001/060380	AU	36949/01	EP	1299108	US	2002010142

END OF ANNEX